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CHEMICAL PROCESS

The present invention relates to a process for the preparation of fluorohaloalkane compounds such as [^{18}F]bromofluoromethane. [^{18}F]Fluorohaloalkanes are important reagents for performing O-, N-, and S-[^{18}F]fluoroalkylations and are commonly used to radiolabel radioligands for use in positron emission tomography (PET) studies.

[^{18}F]Fluorohaloalkanes have previously been prepared by nucleophilic displacement, by [^{18}F]F$^-$, of a leaving group from a suitable precursor compound. Thus, for example Zhang *et al*, Applied Radiation and Isotopes 57, 335-342 (2002), describes synthesis of [^{18}F]fluoroethyl bromide by nucleophilic displacement of 2-trifluoromethanesulphonyloxy ethylbromide with [^{18}F]F$^-$ and Seung-Jun *et al* Applied Radiation and Isotopes (1999), 51, 293-7 describes an analogous synthesis of 3-[^{18}F]fluoropropylbromide. A similar method is described in Comagic *et al* Applied Radiation and Isotopes (2002), 56, 847-851 wherein 2-bromo-1-[^{18}F]fluoroethane is prepared by nucleophilic displacement of 1,2-dibromoethane with [^{18}F]F$^-$.

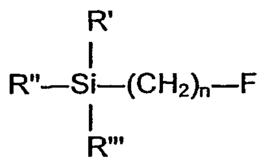
In view of the importance of [^{18}F]Fluorohaloalkanes as radiolabelling reagents, there exists the need for synthetic methods for their preparation in good radiochemical yield and in which isolation of the product is more readily achievable. Furthermore, there is also a need for such synthetic methods which are amenable to automation.

Therefore, according to the present invention, there is provided a process for preparation of a fluorohaloalkane of formula (I)

$$X—(CH_2)_n—F \qquad (I)$$

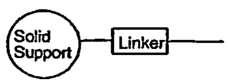
wherein X is halo and n is an integer of from 1 to 6; which comprises:

reaction of the corresponding organosilicon compound of formula (II):



(II)

wherein n is as defined for the compound of formula (I); and R', R", and R'" are independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl; and R" may alternatively be the group:



;

with a compound of formula (III):

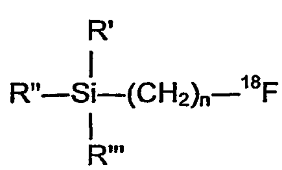
$$XY \qquad (III)$$

wherein X is as defined for the compound of formula (I) and Y is halo.

In a preferred aspect of the invention, the fluorohaloalkane of formula (I) is a [^{18}F]fluorohaloalkane. Therefore, according to a further aspect of the present invention, there is provided a process for preparation of a [^{18}F]fluorohaloalkane of formula (Ia)

$$X\text{—}(CH_2)_n\text{—}^{18}F \qquad (Ia)$$

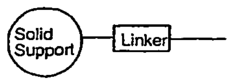
wherein X is halo and n is an integer of from 1 to 6; which comprises: reaction of the corresponding organosilicon compound of formula (IIa):



(IIa)

wherein n is as defined for the compound of formula (Ia); and R', R", and R'" are independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl; and

R" may alternatively be the group:



;

with a compound of formula (III):

$$XY \qquad (III)$$

wherein X is as defined for the compound of formula (Ia) and Y is halo.

Examples of formula (I) which may be prepared using the present process, include fluorobromomethane, fluoroiodomethane, fluorobromoethane, fluoroiodoethane, fluorobromopropane, and fluoroiodopropane, each of which is suitably prepared in [^{18}F]-labelled form.

The reaction of a compound of formula (II) or (IIa) with a compound of formula (III) may be performed in the presence of a catalyst, suitably a tetra (C_{1-6} alkyl) ammonium salt, such as a tetra (C_{1-6} alkyl) ammonium fluoride salt, for example tetrabutylammonium fluoride or tetraethylammonium fluoride; and in a suitable solvent for example acetonitrile or an alcohol such as methanol or ethanol at elevated temperature, for example 50°C to 150°C, suitably 70°C to 120°C.

The resulting compound of formula (I) or (Ia) may be isolated from the reaction mixture, for example, by distillation followed by chromatography, suitably gas or liquid chromatography. In a preferred isolation method, the crude reaction mixture is distilled and the distillate is then passed under a stream of inert gas, such as helium, through a temperature controlled GC column packed with silica gel.

The resulting compound of formula (I) or (Ia) may also be converted to a corresponding fluoroalkylsulphonyl ester of formula (V) or (Va) respectively:

$$R^1SO_2\text{-}O\text{—}(CH_2)_n\text{—}F \qquad (V)$$
$$R^1SO_2\text{-}O\text{—}(CH_2)_n\text{—}{}^{18}F \qquad (Va)$$

wherein n is as defined for the compound of formula (I) or (Ia), and R^1 is selected from C_{1-6} alkyl (for example, methyl), C_{1-6} perfluoroalkyl (for example, trifluoromethyl), aryl (for example, phenyl), tolyl (for example, *para*-tolyl), perfluoroaryl (for example, perfluorophenyl), and perfluorotolyl (for example, perfluoro *para*-tolyl). Thus, for example a $[^{18}F]$fluorohaloalkyl compound of formula (Ia) may be converted to a $[^{18}F]$fluoroalkyltosylate of formula (Va) such as $[^{18}F]$fluoromethyltosylate. Fluoroalkylsulphonyl esters of formulae(V) and (Va) are also useful as fluoroalkylating agents.

Conversion of a compound of formula (I) or (Ia) to a compound of formula (V) or (Va) respectively, may be effected by reaction with the appropriate sulphonic acid of formula R^1SO_2OH or a salt thereof, such as a silver salt. Depending on the particular compound to be prepared, this conversion may be performed in solution phase, or in gaseous phase, for example by methods analogous to those described by Iwata *et al*, Applied Radiation and Isotopes, 57 (2002), 347-352.

The resulting compound of formula (I) or (Ia), or a corresponding compound of formula (V) or (Va) as described above, may be used in the preparation of a fluoroalkyl ligand or radiotracer, for example a $[^{18}F]$fluoroalkylated radioligand or $[^{18}F]$-radiotracer suitable for use in a PET study. Examples of $[^{18}F]$fluoroalkylated radioligands and $[^{18}F]$-radiotracers which may be prepared using the compounds of formula (Ia) or (Va) include 2-(1,1-dicyanopropen-2-yl)-6-(2-$[^{18}F]$-fluoroC_{1-6}alkyl)-methylamino)naphthalene (for example, 2-(1,1-dicyanopropen-2-yl)-6-(2-$[^{18}F]$-fluoroethyl)-methylamino)naphthalene, FDDNP), 3-(2'-$[^{18}F]$fluoroC_{1-6}alkyl)spiperone (for example 3-(2'-$[^{18}F]$fluoroethyl)spiperone), $[^{18}F]$[2-fluoroC_{1-6}alkoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine (for example, $[^{18}F]$[2-fluoromethoxy-5-(5-trifluoromethyl-tetrazol-1-yl)-benzyl]-([2S,3S]-2-phenyl-piperidin-3-yl)-amine), 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-8-(3-$[^{18}F]$fluoroC_{1-6}alkyl)-nortropane (for example, 2-beta-carbomethoxy-3-beta-(4-iodophenyl)-8-(3-$[^{18}F]$fluoropropyl)-nortropane, $[^{18}F]$fluoroC_{1-6}alkylflumazenil (for example, $[^{18}F]$fluoroethylflumazenil),

[^{18}F]fluoroC_{1-6}alkyl-choline (for example, [^{18}F]fluoromethyl-choline or [^{18}F]fluoroethyl-choline), O-2[^{18}F]fluoroalkyl tyrosine (for example O-2[^{18}F]fluoroethyl tyrosine or O-2[^{18}F]fluoropropyl tyrosine), and 1-amino-3-[^{18}F]-fluoroalkylcyclobutane-1-carboxylic acid (for example, 1-amino-3-[^{18}F]-fluoromethylcyclobutane-1-carboxylic acid, (FMACBC)). Other [^{18}F]fluoroalkylated radioligands and [^{18}F]-radiotracers which may be prepared using the compounds of formula (Ia) or (Va) include [^{18}F]-benzyl derivatives.

In the compounds of formulae (I), (Ia), (II), and (IIa), n is preferably 1, 2, or 3 such that the fluorohaloalkane prepared in the process is a fluorohalomethane, fluorohaloethane, or fluorohalopropane.

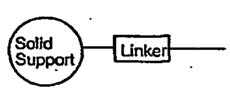
Throughout the specification, the term "halo" means fluoro, chloro, iodo, or bromo.

In the compounds of formulae (I), (Ia), and (III), X is halo, and is preferably bromo or iodo.

In the compounds of formula (III), Y is halo, preferably bromo or iodo, and is preferably the same as X, such that the compound of formula (III) is preferably Br_2 or I_2.

In the compounds of formula (II) and (IIa), R', R", and R"' are suitably selected from C_{1-6}alkyl and C_{1-6}haloalkyl, more suitably C_{1-4}alkyl and C_{1-4}haloalkyl, for example methyl, ethyl, propyl, and isopropyl, typically methyl.

Where R" is the group:



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the "Solid Support" may be any suitable material which is insoluble in any solvents to be used in the process but to which the "Linker" and/or compound of formula (II) or (IIa) can be covalently bound. Examples of suitable solid support include polymers such as polystyrene (which may be block grafted, for example, with

polyethylene glycol), polyacrylamide, and polypropylene or glass or silicon suitably coated with such a polymer. The solid support may be in the form of small discrete particles such as beads or pins, or as a coating on the inner surface of a cartridge or on a microfabricated vessel; and

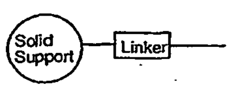
the "Linker" may be any suitable organic group which serves to space the reactive site sufficiently from the solid support structure so as to maximise reactivity. Suitably, the Linker comprises an organic group of from 1 to 12 carbon atoms and from 0 to 6 heteroatoms selected from oxygen, nitrogen, and sulphur. Examples of such linkers are well known to those skilled in the art of solid-phase chemistry, but include phenyl(C_{1-6}alkyl) and phenyl.

Certain of the compounds of formula (II) and (IIa) are novel and thus form a separate aspect of the invention.

Accordingly, there is provided a compound of formula (II):

$$\begin{array}{c} R' \\ | \\ R''\text{—}Si\text{—}(CH_2)_n\text{—}F \\ | \\ R''' \end{array} \qquad \text{(II)}$$

wherein n is an integer of from 1 to 6; and
R' and R''' are independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl; and
R'' is the group:

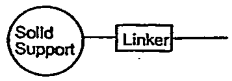


Further, there is provided a compound of formula (IIa):

$$\begin{array}{c} R' \\ | \\ R''\text{—}Si\text{—}(CH_2)_n\text{—}{}^{18}F \\ | \\ R''' \end{array} \qquad \text{(IIa)}$$

wherein n is an integer of from 1 to 6; and

R', R", and R''' are independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl; and R" may alternatively be the group:



Compounds of formula (II) or (IIa) may be prepared from the corresponding compound of formula (IV):

$$R''\text{—}\underset{\underset{R'''}{|}}{\overset{\overset{R'}{|}}{Si}}\text{—}(CH_2)_n\text{—}L \qquad \text{(IV)}$$

wherein n, R', R", and R''' are as defined for the compound of formula (II) or (IIa) and L is a leaving group;

by reaction with a source of F^-, preferably $^{18}F^-$, suitably an alkali metal fluoride salt such as $Na^{18}F$, $K^{18}F$, or $Cs^{18}F$, tetraalkylammonium ^{18}F fluoride, or tetraalkylphosphonium ^{18}F fluoride.;

in the presence of a phase transfer catalyst, suitably 18-crown-6 or a cryptand such as Kryptofix 2.2.2., Kryptofix 2.2.2B., Kryptofix 2.2.1. (all available from Aldrich). The reaction may be performed in a suitable solvent such as acetonitrile and at elevated temperature, suitably 50°C to 100°C.

The leaving group, L, in the compound of formula (IV) is suitably a sulphonyl ester group i.e. $-OSO_2R^2$ wherein R^2 is selected from C_{1-6} alkyl (for example, methyl), C_{1-6} perfluoroalkyl (for example, trifluoromethyl), aryl (for example, phenyl), tolyl (for example, *para*-tolyl), perfluoroaryl (for example, perfluorophenyl), and perfluorotolyl (for example, perfluoro *para*-tolyl).

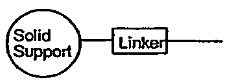
Certain of the compounds of formula (IV) are novel, and therefore according to a

further aspect of the invention there is provided a compound of formula (IV):

$$\begin{array}{c} \quad\ \ R' \\ \quad\ \ | \\ R''\text{—}Si\text{—}(CH_2)_n\text{—}L \\ \quad\ \ | \\ \quad\ \ R''' \end{array} \qquad \text{(IV)}$$

wherein n is an integer of from 1 to 6;

R', R", and R"' are independently selected from C_{1-6} alkyl and C_{1-6} haloalkyl; and R" may alternatively be the group:



;

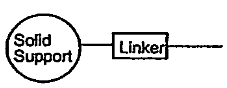
L is a group $-OSO_2R^2$ wherein R^2 is selected from C_{1-6} alkyl, C_{1-6} perfluoroalkyl, aryl, perfluoroaryl, tolyl, and perfluorotolyl;

provided that:

(a) when R" is C_{1-6} alkyl or C_{1-6} haloalkyl, n is not 1; and

(b) when R" is C_{1-6} alkyl or C_{1-6} haloalkyl and n is 2 to 6, L is not $-OSO_2CH_3$ or $-OSO_2$(*para*-methyl)phenyl.

Compounds of formula (IV) in which R" is the group



are a particularly useful class of intermediates and thus form a separate aspect of the invention.

Compounds of formula (IV) are either commercially available (for example, from Aldrich), or a readily prepared from commercially available starting materials using methods available to the person skilled in the art. In one suitable method, the compound of formula (IV) is prepared by reaction of the corresponding azide with the appropriate sulphonic acid or a salt thereof, for example using methods analogous to those described in Al-Busafi *et al*, Tetrahedron Letters, 39, 12 (1998).

The invention will now be illustrated by way of the following Example.

Example

Preparation of [^{18}F]fluorobromomethane

Trimethylsilylmethyl trifluoromethanesulphonate (Aldrich) (5mg) in acetonitrile (1ml) was added to fully dried $^{18}F^{-}$/Kryptofix 2.2.2 complex prepared by standard methods, for example as described in Hammacher et al, J. Nuclear Medicine, 27, 235-8 (1986). The mixture was heated at 75° C for 5 minutes. Tetrabutylammonium fluoride (16mg) in acetonitrile (0.5ml) and bromine (8mg) in methanol (0.5ml) were added to the reaction mixture. The reaction vessel was then sealed and heated at 110°C for 3 to 4 minutes.

[^{18}F]fluorobromomethane produced was then distilled from the vessel at the same temperature. The distillate containing [^{18}F]fluorobromomethane was passed under a stream of helium through a temperature controlled GC column (7.8 x 80 mm) packed with silica gel (70 to 270 mesh, Aldrich). The output from the GC column was examined by a radioactive detector and the fraction with a retention time identical to that of authentic bromofluoromethane was directed to a cooled trapping vial containing a suitable solvent. Suitable solvents include acetonitrile, N,N-dimethylformamide, dimethylsulphoxide, tetrahydrofuran, acetone, acetic acid, and chlorobenzene. Other fractions were vented to waste. The overall radiochemical yield for [^{18}F]fluorobromomethane from [^{18}F]fluoride was 55-70% and the total time for the preparation was approximately 45 minutes from the end of radionuclide production.